IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

SMITH KLINE & FRENCH LABORATORIES LIMITED and SMITHKLINE BEECHAM CORPORATION d/b/a GLAXOSMITHKLINE, Plaintiffs, v. TEVA PHARMACEUTICALS USA, INC., Defendant.	)	Civil Action No. 05-197-GMS **PUBLIC VERSION**

PLAINTIFF'S PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW

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Dated: February 7, 2007

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Plaintiffs Smith Kline & French Laboratories Limited and SmithKline Beecham Corporation d/b/a GlaxoSmithKline (collectively "GSK") set forth below their proposed findings of fact and conclusions of law concerning the validity of claim 3 of U.S. Patent No. 4,824,860 ("the '860 patent"). In summary, defendant Teva Pharmaceuticals USA, Inc. ("Teva") has failed to carry its burden of proving by clear and convincing evidence that (1) the prior art anticipates claim 3 of the '860 patent either expressly or inherently; and (2) that the subject matter of claim 3 of the '860 patent would have been obvious to one of ordinary skill in the art at the time of the invention in view of the prior art references and knowledge in the field under the test set forth in *Graham v. John Deere*, 383 U.S. 1, 17 (1966).[1/]

PROPOSED FINDINGS OF FACT

I. INTRODUCTION

A. Parties

1. This is a patent infringement action in which GSK contends that Teva infringes claim 3 of U.S. Patent No. 4,824,860 ("the '860 patent").

2. Plaintiff Smith Kline & French Laboratories Limited is a private limited company organized under the laws of England. Plaintiff SmithKline Beecham Corporation is a Pennsylvania corporation, which changed its name from SmithKline Beckman Corporation in 1989. In 2000, both Smith Kline & French Laboratories Limited and SmithKline Beecham Corporation began doing business as GlaxoSmithKline ("GSK") after GlaxoSmithKline plc acquired their corporate parent, SmithKline Beecham plc. *See* Statement of Uncontested Facts,

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1/ Pursuant to the Stipulation and Order Regarding the Post-Trial Briefing Schedule entered by the Court on January 17, 2007 [D.I. 167], as amended on January 31, 2007 [D.I. 171], the parties will submit separate briefs and proposed findings of fact and conclusions of law concerning Teva's claim that the '860 patent is unenforceable for inequitable conduct.

Ex. 1 to Proposed Pretrial Order entered Nov. 3, 2006 [D.I. 137] (hereinafter "Stipulated Facts") ¶¶ 1-4. The term GSK is used throughout this document to refer to the two plaintiffs, individually and collectively.

3. Today GSK is a pharmaceutical company headquartered in the United Kingdom with certain operations based in the United States. It is a recognized industry leader with an estimated seven percent of the world's pharmaceutical market. It sells over 100 branded pharmaceutical products throughout the world. *See* GSK 2005 Annual Global Report (PTX 311).[2/]

4. Defendant Teva is a Delaware corporation that is in the business of developing and manufacturing generic pharmaceuticals. *See* Trial Tr. 62:14-19; 66:2-5 (Testimony of Deborah Jaskot).[3/]

B. GSK's Patents and REQUIP®

5. GSK markets a drug called REQUIP®. The active ingredient in REQUIP is ropinirole hydrochloride. *See* Stipulated Facts ¶ 9. Ropinirole hydrochloride is a salt form of ropinirole. Throughout this document, as was the case at trial, the terms ropinirole and ropinirole hydrochloride are used interchangeably.

6. REQUIP has been approved by the United States Food and Drug Administration ("FDA") for the following indications: (1) treatment of the signs and symptoms of idiopathic Parkinson's Disease; and (2) treatment of moderate-to-severe primary Restless Legs Syndrome

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2/ Copies of the trial exhibits have been submitted under separate cover.

3/ For ease of reference, the abbreviation "Trial Tr.," is used throughout this document to refer to the trial transcript, followed by the line and page numbers from the transcript and, where applicable, the name of the testifying witness in parentheses. A copy of the trial transcript is attached hereto as Exhibit A.

("RLS"). *See* Stipulated Facts ¶ 10. REQUIP has been approved by the FDA for treating Parkinson's Disease since 1997 and for RLS since 2005. *Id.*

7. GSK is the owner of the '860 patent. *See* Stipulated Facts ¶ 10.[4/] On April 25, 1989, the '860 patent issued from U.S. Patent Application No. 07/196,653, which was filed on May 19, 1988. The '860 patent claims priority, under 35 U.S.C. § 119, to U.K. Patent Application No. 8712073, filed May 21, 1987. The '860 patent identifies David A. A. Owen as the sole inventor and is assigned on its face to Smith Kline & French Laboratories Limited. *See* '860 patent (PTX 35); Stipulated Facts ¶¶ 19-21.

8. Claim 3 of the '860 patent is a method claim directed to the use of ropinirole hydrochloride to treat Parkinson's Disease. *See* '860 patent, Col. 8:10-14 (PTX 35).

9. GSK is also the owner of U.S. Patent No. 4,452,808 ("the '808 patent"). *See* Stipulated Facts ¶ 23. Claim 5 of the '808 patent is a claim directed to the compound ropinirole hydrochloride. *See* '808 patent, Col. 10: 3-4 (PTX 13).

C. ANDA Litigation

10. Teva filed Abbreviated New Drug Application No. 77-460 (as amended) (hereinafter "Teva's ANDA") seeking approval from the FDA to market a generic version of REQUIP for treatment of the signs and symptoms of idiopathic Parkinson's Disease. As part of Teva's ANDA, Teva certified, pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), that the '808 and the '860 patents were "invalid or would not be infringed." *See* Stipulated Facts ¶ 12; Teva's Paragraph IV Certification (PTX 53).

11. On April 6, 2005, GSK timely filed the current lawsuit for infringement of the '808 and '860 patents. *See* Stipulated Facts ¶ 14.

[4/] Teva stipulated that GSK is the owner of the '860 patent without prejudice to its defenses and counterclaims relating to inequitable conduct, which, as noted in footnote 1 above, will be addressed in separate briefing.

12. The submission by Teva of Teva's ANDA constituted an act of infringement, under 35 U.S.C. § 271(e)(2), of claim 5 of the '808 patent and claim 3 of the '860 patent to the extent those claims are valid and enforceable. *See* Stipulated Facts ¶ 16; Joint Stipulation and Proposed Order entered June 26, 2006 [D.I. 61] ¶¶ 1, 3.

13. Less than a week before trial, Teva withdrew its Paragraph IV certification with respect to the '808 patent and agreed to convert that certification to a Paragraph III certification. *See* Stipulation to Partially Dismiss Claims Related to U.S. Patent No. 4,452,808 (Without Prejudice) entered December 14, 2006 [D.I. 162]. Teva therefore is no longer challenging the validity and enforceability of the '808 patent, and the parties have dismissed their respective claims and counterclaims relating to the '808 patent.

14. In light of Teva's abandonment of its challenge to the '808 patent and its stipulation of infringement of claim 3 of the '860 patent, the only remaining issues to be resolved at trial were: (1) Teva's contention that claim 3 of the '860 patent is invalid based on anticipation and/or obviousness; and (2) Teva's contention that the '860 patent is unenforceable for inequitable conduct (which, as noted in footnote 1 above, will be addressed in separate briefing).

D. Trial

15. A three-day bench trial was held from December 18, 2006, through December 20, 2006.

16. Teva presented three live witnesses at trial:

a. Ms. Deborah Jaskot is the Vice President of Regulatory Affairs at Teva. Ms. Jaskot provided background information regarding Teva and its process for identifying and developing potential generic drugs.

b. Dr. Daniel Tarsy is the Vice Chair of the Department of Neurology and the Director of the Parkinson's Disease and Movement Disorder Center at Beth Israel Deaconness Medical Center in Boston, Massachusetts. He is also a Professor of Neurology at Harvard Medical School. Dr. Tarsy testified about the symptoms of Parkinson's Disease and the available treatments, including REQUIP.

c. Dr. John Paul Long is a Professor *Emeritus* of Pharmacology from the University of Iowa. Dr. Long is an award-winning professor who devoted approximately 17 years to the study of interactions with dopamine receptors and potential anti-Parkinsons' agents, a field in which he published extensively. Dr. Long's testimony addressed the issue of whether claim 3 of the '860 patent was anticipated or obvious.

17. GSK also offered three live witnesses at trial:

a. Dr. Lewis Sudarsky is an Associate Physician in Neurology and the Director of the Movement Disorder Program at Brigham and Women's Hospital in Boston. He is also an Associate Professor of Neurology at Harvard Medical School. Dr. Sudarsky provided background information on Parkinson's Disease and available treatments, including REQUIP.

b. Dr. Paul Bartlett is Professor *Emeritus* of Chemistry at the University of California, Berkeley. Dr. Bartlett offered testimony on the differences between compounds in the indolone series, such as ropinirole hydrochloride, and compounds in the indole series.

c. Dr. Peter Jenner is a Professor of Pharmacology and the Director of the Neurodegenerative Diseases Research Centre at King's College London in London, United Kingdom. Dr. Jenner specializes in neuropharmacology, with a particular focus

on dopamine systems and Parkinson's Disease. He has worked in the field of Parkinson's Disease for 32 years, and he has lectured extensively and published approximately 1000 articles in that area. Dr. Jenner's testimony addressed the issue of whether claim 3 of the '860 patent was anticipated or obvious.

18. Both Teva and GSK also made available experts to address the issue of commercial success. During trial, the parties proposed, and the Court agreed, that the Court would receive in evidence (subject to any objections the parties might elect to pursue in briefing) the expert report and deposition testimony of each of those experts in lieu of live testimony. *See* Trial Tr. 696:8-24.

a. The expert offered by Teva in the area of commercial success is Harry C. Boghigian. Mr. Boghigian is a pharmaceutical company executive and consultant and has a Bachelor of Science degree from the University of New Hampshire, Whittemore School of Business.

b. The expert offered by GSK in the area of commercial success is Dr. Christopher C. Vellturo. Mr. Vellturo is the founder and president of Quantitative Economic Solutions, LLC, an economic consulting firm. He received a Ph.D. in Economics from the Massachusetts Institute of Technology in 1989, has performed extensive economic analyses in a wide range of industries, and has provided expert testimony in the context of mergers and acquisitions, antitrust litigation, and intellectual property litigation.

19. The Court also received a joint post-trial submission of deposition designations from GSK and Teva for several fact witnesses who did not testify at trial.[5/]

20. At the conclusion of the trial, the Court noted that the two "preeminent authorities" in pharmacology that had testified before it, Drs. Jenner and Long, fundamentally agreed on the state of the art at the relevant time in the important ways. Trial Tr. 718:3-9. Finding that the case was "not close," Trial Tr. 711:11-18, and that the testimony contained in the deposition designations (as described by Teva's counsel) would likely be cumulative, Trial Tr. 714:20-715:5, the Court announced a general verdict in favor of GSK on the issue of whether claim 3 of the '860 patent was anticipated or obvious in light of the prior art, *see* Trial Tr. 722:9-18. In so doing, the Court recognized the value of rendering a decision when the evidence and the impression of the witnesses "is fresh in the Court's mind." Trial Tr. at 714:1-13.

21. The Court requested that GSK submit findings of fact and conclusions of law in support of its general verdict. *See* Trial Tr. 721:1-8. The Court also provided Teva with the opportunity to respond to such findings and conclusions and reserved the specific articulation of findings of fact and conclusions of law until after its review of all of the parties' submissions, including the deposition designations. *See* Trial Tr. 719:5-15; 721:1-8.

22. The Court issued the following ruling pursuant to Fed. R. Civ. P. 52(a) in favor of GSK:

> ORAL RULING (GENERAL VERDICT): FINDING THAT Teva has failed to prove by clear and convincing evidence: (1) that the prior art anticipates claim 3 of the '860 patent either expressly or inherently; and (2) that the subject matter of claim 3 of the '860 patent would have been obvious to one of ordinary skill in the art at the time of the invention in view of the prior art references and knowledge

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5/ None of the witnesses whose testimony was submitted by deposition designation, aside from the commercial success experts Dr. Vellturo and Mr. Boghigian, was disclosed by either party under Rule 26(a)(2) of the Federal Rules of Civil Procedure or in the Proposed Pretrial Order as an individual who may be used to present expert testimony.

> in the field under the test set forth in *Graham v. John Deere*, 383 U.S. 1, 17 (1966). The Court shall reserve the specific articulation of its findings of fact and conclusions of law for a memorandum decision which shall be issued at a later date. The parties shall submit a briefing schedule regarding inequitable conduct and proposed findings of fact and conclusions of law.

Oral Ruling (December 20, 2006).

II. BACKGROUND

A. Parkinson's Disease and Available Treatments

23. At trial, Dr. Tarsy and Dr. Sudarsky—esteemed neurologists offered as experts by Teva and GSK, respectively—testified about Parkinson's Disease and its available treatments, including REQUIP. Drs. Sudarsky and Tarsy were largely in agreement concerning the symptoms of Parkinson's Disease, the range of treatments and their respective advantages and disadvantages, and the usefulness and effectiveness of REQUIP for the treatment of Parkinson's Disease.

24. Parkinson's Disease is a progressive degenerative disease for which there is no cure. *See* Trial Tr. 102:13-103:11; 105:6-7 (Tarsy). Parkinson's Disease is estimated to affect a million patients in North America, and it has an annual incidence of around 50,000 cases a year. *See* Trial Tr. 412:8-14 (Sudarsky).

25. Parkinson's Disease is characterized by the degeneration, or dying off, of dopamine nerve cells in the brain. *See* Trial Tr. 103:15-104:2 (Tarsy). Dopamine is a neurotransmitter that conveys information or messages from one nerve cell to another nerve cell. *See* Trial Tr. 104:3-10 (Tarsy). The loss of these dopamine-generating nerve cells leads to problems with everyday motor functions such as walking, facial expressiveness, and the volume of one's voice. *See* Trial Tr. 104:11-105:5 (Tarsy).

26. The symptoms of Parkinson's Disease include tremor, slowness of movement (called "bradykinesia"), rigidity or stiffness of muscles, gait disorder, and unstable balance. *See* Trial Tr. 102:13-103:11 (Tarsy).

27. The treatment of Parkinson's Disease is a difficult endeavor. *See* Trial Tr. 124:24-125:1; 135:16-21 (Tarsy). Patients are typically treated for many years. *See id.*

28. "There is no one-size-fits-all medication" for the treatment of Parkinson's Disease. Trial Tr. 415:16-416:24 (Sudarsky). The decision of which drugs to prescribe to a particular patient is based on the individual case, because responses to medication can be erratic and unpredictable and patients can have variable responses. *See* Trial Tr. 125:5-15 (Tarsy). It is therefore useful to have a number of drugs to choose from in treating Parkinson's Disease. *See* Trial Tr. 125:16-18; 125:24-126:1 (Tarsy); 430:15-22 (Sudarsky).

29. The principal therapeutic strategy for treating Parkinson's Disease involves replacing the dopamine that is not made in sufficient quantities as the dopamine-producing cells are lost. *See* Trial Tr. 411:21- 412:7 (Sudarsky). Levodopa or "L-dopa", which was introduced in the late 1960's, is the gold standard in Parkinson's Disease treatment. *See* Trial Tr. 105:17-21; 106:5-12 (Tarsy). Levodopa is a dopamine precursor that is converted into dopamine in the brain. *See* Trial Tr. 106:23-107:3 (Tarsy); 443:20-444:1 (Sudarsky).

30. In a large percentage of patients, long-term treatment with levodopa is associated with the development of motor complications, such as dyskinesias (involuntary movements) and motor fluctuations. *See* Trial Tr. 128:5-17 (Tarsy); 416:4-20 (Sudarsky). Patients often have difficulties maintaining a stable response to levodopa and may have "abrupt off periods or freezing of gait." Trial Tr. 415:4-416:24 (Sudarsky).

31. Another group of anti-Parkinson's drugs, known as "dopamine agonists," consists of synthetic compounds that act by mimicking the effect of dopamine and directly activating dopamine receptors in the brain. *See* Trial Tr. 106:16-18; 107:14-20 (Tarsy).[6/]

32. Ropinirole hydrochloride (REQUIP) is a dopamine agonist compound. *See* Trial Tr. 109:22-25 (Tarsy); 413:17-414:1 (Sudarsky). As such, it provides certain advantages over levodopa. In particular, it is less prone to causing the dyskinesias and motor fluctuations seen with levodopa. *See* 129:5-11; 130:2-10 (Tarsy).

33. Adjunctive (or "add-on") therapy occurs when a dopamine agonist is used in the supporting role to help stabilize some of motor fluctuations that occur with levodopa. *See* Trial Tr. 418:1-13 (Sudarsky). REQUIP is useful as an adjunctive therapy for Parkinson's Disease patients who are on levodopa. *See* Trial Tr. 421:18-22 (Sudarsky). REQUIP is among the drugs recommended by the American Academy of Neurology in its practice parameter for the management of motor fluctuations in Parkinson's Disease as an adjunctive therapy with levodopa. *See* Trial Tr. 420:5-421:7 (Sudarsky); Pahwa, R., et al., *Practice Parameter: Treatment of Parkinson Disease with motor fluctuations and dyskinesia (an evidence-based review)*, Neurology, 66(1), 983-95 (2006) (PTX 297).

34. REQUIP can also be used successfully alone as an initial single drug therapy (or "monotherapy"). *See* Trial Tr. 422:16-424:9 (Sudarsky). As demonstrated by a study (known as the "'056 study") published in the New England Journal of Medicine in 2000, early Parkinson's Disease can be managed successfully for up to five years with reduced risk of dyskinesia by

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[6/] A "dopaminergic" compound is a compound that works like dopamine. *See* Trial Tr. 529:12-16 (Jenner). A dopamine agonist, such as ropinirole hydrochloride, is a molecule that will interact with a dopamine receptor and mimic the effects of dopamine. *See* Trial Tr. 546:1-4 (Jenner); 168:1-7 (Long). A dopamine antagonist, on the other hand, is a molecule that will interact with the receptor in a different way and block the effects of dopamine or a dopamine agonist. *See* Trial Tr. 545:9-14 (Jenner).

initiating treatment with ropinirole hydrochloride alone and supplementing it with levodopa if necessary. *See* Trial Tr. 423:22-424:9 (Sudarsky); Rascol, et al., *A five-year study of the incidence of dyskinesia in patients with early Parkinson's Disease who were treated with ropinirole or levodopa,* N. Engl J. Med., 342, 1484-91 (2000) (PTX 255). REQUIP is among the drugs recommended by the American Academy of Neurology in its practice parameter for initial monotherapy to delay the motor complications associates with levodopa. *See* Trial Tr. 425:15-426:19 (Sudarsky); Miyasaki, et al., *Practice parameter: Initiation of treatment for Parkinson's Disease: An evidence-based review*, Neurology, 58(1), 11-17 (2002) (PTX 265).

35. There are two main categories of dopamine agonists: "ergoline-type" dopamine agonists, including bromocriptine and pergolide, and "non-ergoline-type" dopamine agonists, including ropinirole hydrochloride (REQUIP) and pramipexole (MIRAPEX®). *See* Trial Tr. 130:11-24 (Tarsy); 413:17-414: 1 (Sudarsky).

36. Ergoline-type dopamine agonists are associated with serious side effects, such as pulmonary fibrosis and heart valve changes, and are not frequently prescribed. Trial Tr. 428:1-25 (Sudarsky). As a result of these side effects, some physicians, including Teva's expert, Dr. Tarsy, do not prescribe ergoline-type dopamine agonists. *See* Trial Tr. 130:25-131:9 (Tarsy). These serious side effects have not been reported for the non-ergoline dopamine agonists such as REQUIP. *See* Trial Tr. 429:1-4 (Sudarsky).

37. REQUIP and MIRAPEX are the two most frequently used dopamine agonists for the treatment of Parkinson's Disease. *See* Trial Tr. 131:24-132:1 (Tarsy).

38. There is still a need for REQUIP, despite the availability of MIRAPEX, because there are patients who cannot take MIRAPEX who may be treated successfully with REQUIP. *See* Trial Tr. 429:24-430:14 (Sudarsky). For instance, it is not unusual for a patient to

experience side effects with one of the dopamine agonists and not others. *See* Trial Tr. 134:21-135:5 (Tarsy). If a patient exhibits side effects with either MIRAPEX or REQUIP, switching to the other drug can sometimes reduce the severity of those side effects. *See* Trial Tr. 134:15-20 (Tarsy).

39. REQUIP is metabolized by the liver, while MIRAPEX is largely excreted by way of the kidneys. *See* Trial Tr. 133:20-24 (Tarsy); REQUIP Tablet—Prescribing Information at 3 (DTX 221); Mirapex Tablet—Information Booklet at GSK-SUD 000071 (DTX 220). Because of the different ways in which the drugs are eliminated, there are patients for whom one or the other of the drugs is more appropriate. *See* Trial Tr. 133:25-134:3 (Tarsy). For example, REQUIP would be used instead of MIRAPEX for patients with severe kidney disease. *See* Trial Tr. 134:4-8 (Tarsy). It is beneficial for doctors to have an alternative to MIRAPEX for patients with kidney problems, and REQUIP presents such an alternative. *See* Trial Tr. 134:9-14 (Tarsy).

40. REQUIP also has a broad dynamic range (the range of doses over which a drug is incrementally effective). *See* Trial Tr. 430:23-431:16 (Sudarsky). This broad dynamic range is useful because it provides dose flexibility. *See* Trial Tr. 434:6-14 (Sudarsky). It is also useful because, as the motor disability in Parkinson's Disease advances, REQUIP can be given at very high doses to reduce dyskinesias and motor fluctuations. *See* Trial Tr. 432:1- 433:10 (Sudarsky); Mungersdorf M, et al, *High dose therapy with ropinirole in patients with Parkinson's Disease*, J. of Neural Transmission, 1309-1317 (2001) (PTX 261). There is no evidence to support the use of MIRAPEX at a comparably high dose range. *See* Trial Tr. 433:11-23 (Sudarsky).

41. REQUIP is widely prescribed for Parkinson's Disease. *See* Trial Tr. 127:17-23 (Tarsy).

42. In summary, the testifying clinicians for GSK and Teva agreed that: (a) Parkinson's Disease treatment must be individualized, *see* Trial Tr. 125:5-15 (Tarsy); 415:16-416:3 (Sudarsky); (b) it is useful to have a number of drugs to choose from in treating Parkinson's Disease, *see* Trial Tr. 125:16-18; 125:24-126:1 (Tarsy); 430:15-22 (Sudarsky); and (c) REQUIP is a clinically useful and effective drug for the treatment of Parkinson's Disease and is helpful to have available as a therapy, *see* Trial Tr. 126:20-25 (Tarsy); 415:8-14 (Sudarsky).

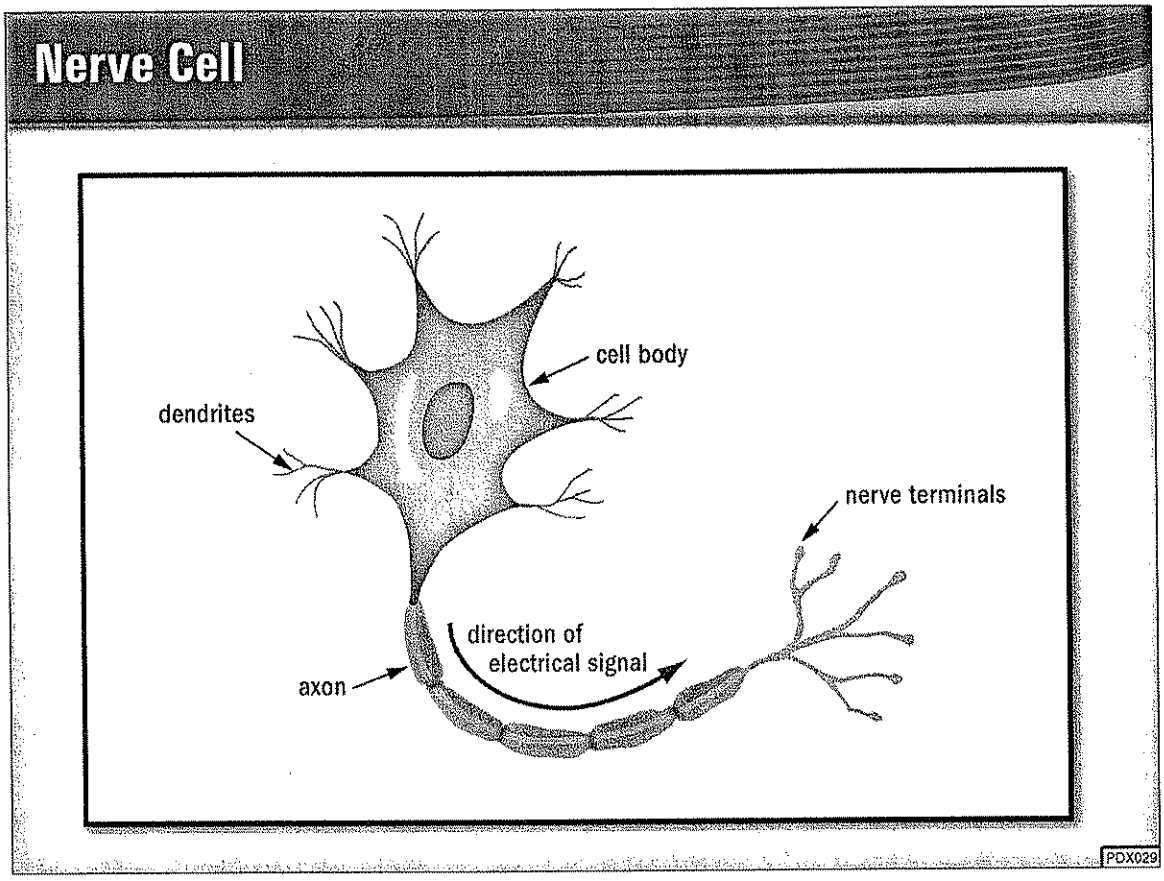
B. The Nervous System, Dopamine, and Dopaminergic Compounds

43. At trial, GSK and Teva presented experts in pharmacology, Dr. Jenner and Dr. Long respectively, who described the workings of the nervous system and the role of dopamine in Parkinson's Disease. *See, e.g.*, Trial Tr. 163:6-172:22 (Long); 535:12-554:1 (Jenner).

44. The human nervous system is composed of two distinct systems: the central nervous system and the peripheral nervous system. *See* Trial Tr. 536:2-9 (Jenner). The central nervous system comprises the brain and the spinal cord. *See* Trial Tr. 536:2-4 (Jenner); 163:6-15 (Long). The peripheral nervous system is composed of the nerve system for all other parts of the body, including organs such as the kidneys and the heart, the gut, and the liver. *See* Trial Tr. 536:5-9 (Jenner).

45. Both the central and peripheral nervous system are formed by the interconnection of nerve cells. A diagram demonstrating the structure of a nerve cell is provided on the following page as Figure 1.

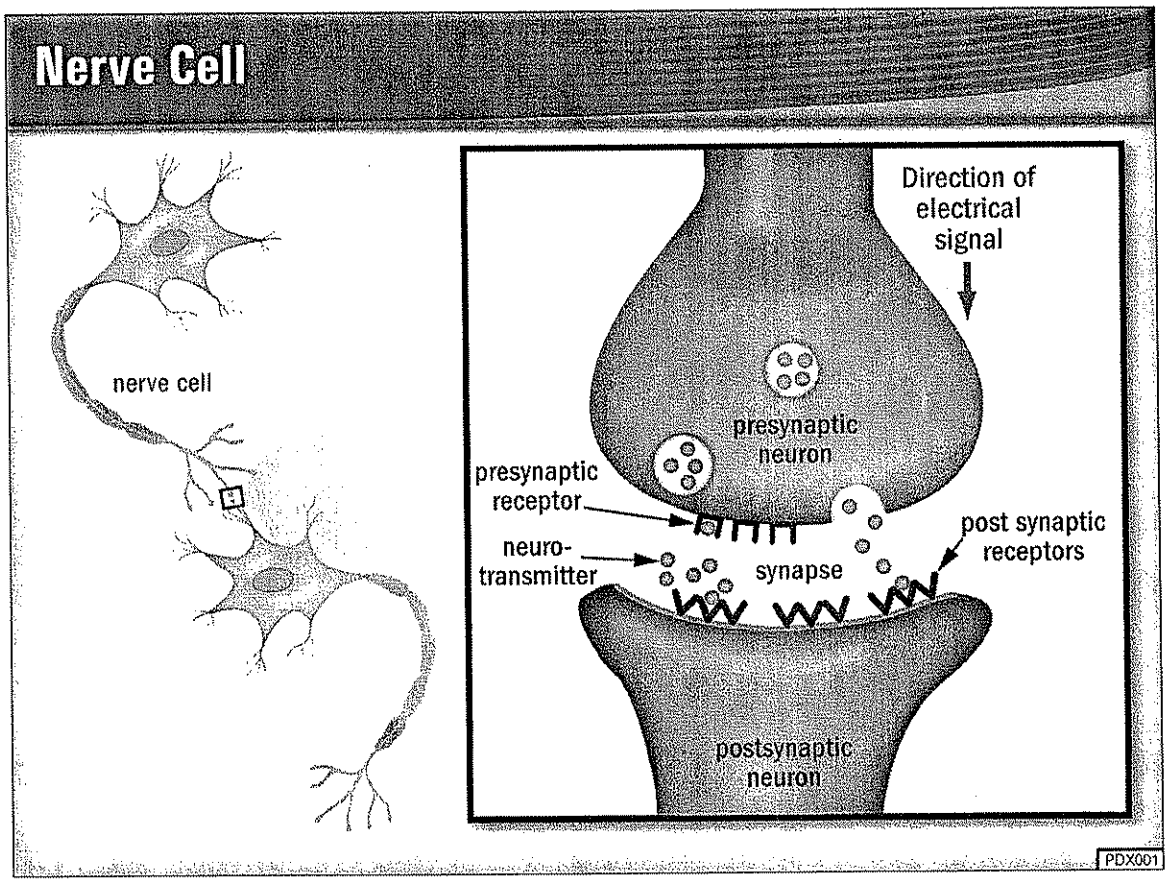
Figure 1:



46. The basic structure of a nerve cell consists of a cell body that has projections extending from it referred to as dendrites. *See* Trial Tr. 536:18-537:23 (Jenner). Dendrites receive information from other nerve cells. *See id.* A nerve cell also has an axon or sheath, which has a dense branching of nerve terminals that transmits information to other nerve cells. *See id.*

47. Nerves communicate through electrical signals. *See id.* As shown in Figure 2 on the following page, an electrical signal is generated in a nerve cell and travels down the cell through the nerve terminal, where the signal stimulates the release of a neurotransmitter. *See* Trial Tr. 538:25-539:16 (Jenner). A neurotransmitter is a chemical substance, such as dopamine, that conveys messages between adjacent nerve cells. *See* Trial Tr. 535:21-23 (Jenner).

Figure 2:



48. Upon release from the nerve cell, neurotransmitters are released into a gap that separates one nerve cell from the other, called a "synapse" or "synaptic cleft." *See* Trial Tr. 538:25-539:16 (Jenner). Neurotransmitters then diffuse across the synapse and occupy receptors on the next nerve. *See id.* The interaction of the neurotransmitters with these receptors leads to the generation of a new electrical signal in the next nerve, creating a chain of neurotransmission. *See id.*

49. Dopamine is a neurotransmitter that is located in both the peripheral and central nervous systems. *See* Trial Tr. 163:16-21 (Long); 535:21-536:1 (Jenner). The interaction of dopamine with certain dopamine receptors in the central nervous system controls bodily movement. *See* Trial Tr. 165:2:8 (Long).

50. A dopamine receptor is a protein embedded in a nerve cell membrane that recognizes dopamine, resulting in a biochemical change and the subsequent generation of an electrical impulse. *See* Trial Tr. 540:9-13 (Jenner).

51. There are different subtypes of dopamine receptors, including D1 receptors and D2 receptors. *See* Trial Tr. 540:22-25 (Jenner); 293:10-15 (Long). The first description of multiple dopamine receptors was in 1979. *See* Trial Tr. 541:1-8 (Jenner). As of May 1987, it was largely thought that dopamine receptors fell into two major families—those relating to the D1 receptor and those relating to the D2 receptor. *See* Trial Tr. at 559:16-22 (Jenner).[7/] Both D1 and D2 receptors can be found in both the peripheral and central nervous systems. *See* Trial Tr. 541:9-15 (Jenner).

52. Dopamine receptors can be located on the pre-synaptic side of a nerve cell (before the synapse) and on the post-synaptic side of a nerve (after the synapse). *See* Trial Tr. 540:9-21 (Jenner); 165:9-16 (Long). In the peripheral nervous system, D2 receptors are largely located at pre-synaptic sites, and they alter the release of the neurotransmitter norepinephrine. *See* Trial Tr. 542:7-15 (Jenner); 166:3:10 (Long). In the central nervous system, D2 receptors are located both pre-synaptically and post-synaptically. *See* Trial Tr. 542:17-22 (Jenner).

C. Characteristics of Potential Anti-Parkinson's Drugs

53. As describe above, certain dopamine agonist compounds can be used to treat Parkinson's Disease. Dr. Jenner and Dr. Long were in agreement that a dopamine agonist must act on *post-synaptic D2 receptors* in the *central* nervous system to have potential as an anti-Parkinson's agent. *See* Trial Tr. 546:14-19 (Jenner); 165:2-8; 165:24-166:2 (Long).

7/ At the present time, the following subtypes of dopamine receptors are believed to exist: D1, D2, D3, D4, and D5. *See* Trial Tr. 540:22-25 (Jenner).

54. *Pre-synaptic* D2 agonists that act in the central nervous system are not useful for treating Parkinson's Disease. *See* Trial Tr. 544:13-23 (Jenner); 320:11-19 (Long). When pre-synaptic D2 receptors are stimulated, they turn off the production of dopamine, which, in a Parkinson's Disease patient, would increase the symptoms of the disease. *See* Trial Tr. 544:13-24 (Jenner).

55. Dopamine *antagonists* also are not used in Parkinson's Disease treatment. *See* Trial Tr. 331:3-15 (Long); 545:15-25 (Jenner). Blocking dopamine receptors with dopamine antagonists would lead to a further decline in dopamine levels, thereby exacerbating the symptoms of the disease. *See* Trial Tr. 545:15-25 (Jenner); 331:8-15 (Long).

56. In order to treat Parkinson's Disease, a compound must be able to cross what is known as the blood-brain barrier. *See* Trial Tr. 170:22-171:8 (Long).

57. The blood-brain barrier is a group of tightly interlocked cells that line the blood vessels that supply the brain. *See* Trial Tr. 551:2-13 (Jenner). These cells act as a physical barrier to prevent unwanted substances from passing out of the bloodstream and into the brain, where they might have a disruptive effect. *Id.*; Trial Tr. 171:11-16 (Long).

58. The blood-brain barrier is a significant consideration in the development of drugs to treat Parkinson's Disease. This is because medications are typically given orally and must, therefore, pass the blood-brain barrier before they can act on post-synaptic D2 receptors in the brain. *See* Trial Tr. 551:19-552:1 (Jenner).

59. As of May 1987, several factors were known to possibly affect the ability of a compound to pass the blood-brain barrier, including size, electrical charge, the availability of active transport mechanisms, and lipophilicity (the ability of the compound to dissolve in fat). *See* Trial Tr. 552:2-553:9 (Jenner).

60. In summary, Drs. Jenner and Long were in agreement that, as of May 1987, it was known that, in order to qualify as a potential candidate for treating Parkinson's Disease, a dopamine agonist would need to (a) act on post-synaptic D2 receptors; (b) in the central nervous system; and (c) cross the blood-brain barrier.

III. VALIDITY

A. Teva's Validity Defenses

61. Teva has alleged that the '860 patent is anticipated by the '808 patent.

62. Teva has also alleged that the '860 patent is obvious in light of the '808 patent in combination with one or more prior art references. The references on which Teva focused at trial were: (a) Cannon, J.G., et al., *Proposed Dopaminergic Pharmacophore of Lergotrile, Pergolide, and Related Ergot Alkaloid Derivatives,* J. Med. Chem.-Communications to the Editor, 24, 238-40 (1981) ("Cannon 1981 article) (DTX 62); (b) Cannon, J.G., *The Design of Potential Anti-Parkinsonian Drugs: What is the Dopaminergic Pharmacophore in Ergot Alkaloids?,* Proc. Iowa Acad. Sci., 93(4), 169-74 (1986) ("Cannon 1986 article") (DTX 179); and (c) Cannon, J.G., et al, *Preparation and Biological Actions of Some Symmetrically N, N-Disubstituted Dopamines*, J. Med. Chem., 21(3), 248-53 (1978), ("Cannon 1978 article") (DTX 160).

B. One of Ordinary Skill in the Art

63. At trial, the parties offered competing definitions of "one of ordinary skill in the art" for purposes of determining whether claim 3 of the '860 patent is anticipated or obvious. Teva's expert, Dr. Long, testified that one of ordinary skill in the art would have been an individual who has a Ph.D. or an M.D., was involved in dopamine research, and was familiar with both the central and peripheral nervous systems. *See* Trial Tr. 178:7-18 (Long). GSK's

expert, Dr. Jenner, testified that one of ordinary skill in the art would have been someone with a basic education in either chemistry or pharmacology who had some form of higher degree in pharmacology or medicinal chemistry or some years of experience working in medicinal chemistry or pharmacology in an academic or industrial setting. *See* Trial Tr. 554:13-22 (Jenner). The standard offered by Teva and Dr. Long was higher than that offered by GSK and Dr. Jenner in that it required one of ordinary skill in the art to have experience with dopamine research in both the central and peripheral nervous systems.

64. There is a sound basis for adopting GSK's definition of one of ordinary skill in the art over Teva's more stringent standard. Teva's definition appears to be unduly narrow, particularly in light of Dr. Long's admission that "maybe 300-400" people would have met his definition of one of ordinary skill in the art in 1987. Trial Tr. 257:18-22 (Long).

65. In any event, there is no need for the Court to adopt one definition over the other. The differences between the two definitions amount to a distinction without a difference, given that, under either definition, one of ordinary skill in the art would have access to all of the relevant publications, including the contemporaneous publications of Dr. Long, a self-described expert in the field of dopaminergic agents. *See* Trial Tr. 236:18-21 (Long). The outcome of the anticipation and obviousness analyses is the same regardless of which definition is applied.[8/] Therefore, for purposes of this memorandum, the more stringent definition advocated by Teva is applied.

66. Furthermore, the fact deposition testimony Teva submitted by designation does not affect the definition of one of ordinary skill in the art or the outcome of the anticipation and

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8/ Indeed, Dr. Jenner testified at trial that his opinions relating to claim 3 of the '860 patent would not change if Dr. Long's definition of one of ordinary skill in the art were adopted by the Court. *See* Trial Tr. 555:2-4 (Jenner).

obviousness analyses. As noted in footnote 5 above, Teva did not designate any of the fact witnesses on whom it now attempts to rely with respect to this issue as an individual who might present expert testimony at trial in any pretrial filing or disclosure pursuant to Rule 26(a)(2) of the Federal Rules of Civil Procedure. Moreover, testimony about what specific fact witnesses may or may not have known at the time of the invention is irrelevant to the question of whether the invention at issue would have been anticipated or obvious to one of ordinary skill in the art. *See Standard Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985) ("The issue of obviousness is determined entirely with reference to a *hypothetical* 'person having ordinary skill in the art.'") (emphasis in original); *Bausch & Lomb, Inc. v. Barnes-Hing/Hydrocurve, Inc.*, 796 F.2d 443, 447-48 (Fed. Cir. 1986) (finding that the district court erred in its obviousness analysis by substituting the opinion of the inventor for one of ordinary skill in the art).

C. The State of the Art as of May 1987

1. Confusion and Unpredictability Concerning Dopamine Receptors and Receptor Activity

67. During the 1980s, there was a period of "immense change" and "terrible confusion and chaos" over the way in which dopamine receptors should be classified. Trial Tr. 541:1-8 (Jenner).

68. In 1981, Dr. Long and his colleague, Dr. Joseph Cannon, described the literature concerning the classification of dopamine receptors:

> Costall and Naylor have noted that the literature describes numerous dopamine receptor subtypes based upon diverse techniques (behavioral, electrophysiological, biochemical, and others), using vertebrates and invertebrates. Evidence of classification is not always convincing, and correlation between the various subtypes is very difficult. Further, with terminologies ranging from DA-1, DA-2, D_1, D_2, DI, DE, DA_i, DA_e, DA_α, DA_β, D-1, D-2, and even D-3, *the literature seems to be impossibly confusing*.

Cannon J.G., et al., *Future directions in dopaminergic nervous system and dopaminergic agonists*, J. Med. Chem., 24(10), 1113-18 (1981) ("1981 Future Directions" article) (PTX 117) (emphasis added). At trial, Dr. Jenner and Dr. Long both agreed that this portion of the 1981 Future Directions article accurately described the state of knowledge about dopamine receptors at the time. *See* Trial Tr. 296:21-297:12 (Long); 569:13-570:2 (Jenner). Both experts further agreed that there was still confusion regarding the classification of dopamine receptors at the time of the filing of the '860 patent in May 1987. *See* Trial Tr. 296:21-297:24 (Long); 570:3-5 (Jenner).[9/]

69. As of May 1987, one of ordinary skill in the art could not have predicted whether a compound that was a *pre-synaptic* D2 agonist in the *peripheral* nervous system (such as ropinirole hydrochloride) would be a *post-synaptic* D2 agonist in the *central* nervous system. *See* Trial. Tr. 560:3-8 (Jenner). At that time, one of ordinary skill in the art would have thought that the central D2 receptor and peripheral D2 receptor systems were different. *See* Trial Tr. 559:23-560:2 (Jenner).

9/ This confusion is further evidenced by a 1985 article about which Dr. Jenner testified at trial. *See* Kaiser, et al., *Dopamine Receptors: Functions, Subtypes, and Emerging Subtypes*, Med. Res. Rev., 5(2), 145-229 (1985) ("1985 Kaiser article") (DTX 377). The 1985 Kaiser article states: "The topic of dopamine receptors remains an area of ongoing investigation, controversy, and disagreement, although there is clearly a movement toward convergence of earlier dissenting views on the classification of these receptors." *Id.* at 161. Dr. Jenner indicated that this statement "encapsulated the sentiments at that time perfectly." Trial Tr. 668:15-669:3 (Jenner). Dr. Jenner further testified that the 1985 Kaiser article:

> is a fascinating, comprehensive review, it illustrates the wealth of different dopaminergic structures that were being investigated at this time, and it illustrates fully the differences of opinion that occurred over the classification of dopamine receptors [and] over the ability to construct structure/activity relationships and affect the ability of drugs to penetrate through the blood brain barrier.

Trial Tr. 670:8-20 (Jenner).

70. Both Dr. Jenner and Dr. Long testified that one of ordinary skill in the art would have been aware in May 1987 that there were compounds thought to act peripherally, but not centrally, on dopamine receptors. *See* Trial Tr. 560:18-22 (Jenner); 302:6-15 (Long). Examples of such compounds included (-)-3-PPP and transdihydrolisuride. *See* Trial Tr. 560:21-561:2 (Jenner).

71. Moreover, Dr. Long conceded during cross-examination that, as of 1987, testing would be necessary in order to determine if a compound acting on the peripheral D2 receptor would also act on the central D2 receptor:

> Q. Now, Dr. Long, if a compound acts on the peripheral D2 receptor, you would have to test it to determine if it would act on the central D2 receptor. Correct?
>
> A. Correct.
>
> Q. And that was true in 1987. Correct?
>
> A. Correct.

Trial Tr. 311:14-19 (Long). Dr. Long further conceded that, as of 1987, the effect of dopamine agonists on the central nervous system was "yet to be unraveled." Trial Tr. 309:18-310:10 (Long).

72. As of May 1987, one of ordinary skill in the art also would not have equated activity at *pre-synaptic* D2 receptors in the periphery with activity at *post-synaptic* D2 receptors in the brain. *See* Trial Tr. 559:23-560:17 (Jenner).

73. Both Dr. Jenner and Dr. Long acknowledged that there were known compounds as of that time that were active pre-synaptically in the peripheral nervous system but *not* post-synaptically in the central nervous system. *See* Trial Tr. 565:8-566:22 (Jenner); 355:21-356:1 (Long). Compound 10 as described in the 1981 Future Directions article, provides one such example. *See* 1981 Future Directions article at 1116 (PTX 117); Trial Tr. 565:8-15 (Jenner);

355:5-20 (Long). Dr. Long conceded that it was necessary to test a compound that was active pre-synaptically in the periphery in order to determine if it was active post-synaptically in the central nervous system:

> Q. So you knew and, in fact, had reported to the scientific community as of 1981 that there were compounds that were active pre-synaptically in the periphery but were not active post-synaptically in the central nervous system; correct?
>
> A. Yes, there were a few in this category.
>
> Q. And you had to test them to find out?
>
> A. Right.

Trial Tr. 355:21-356:3 (Long).

2. Unpredictability Associated With the Blood-Brain Barrier

74. As of May 1987, the ability of any given compound to cross the blood-brain barrier was unpredictable. *See* Trial Tr. 560:3-17; 594:16-595:13 (Jenner). Dr. Long conceded that a compound needs to be tested in order to determine whether it will cross the blood-brain barrier:

> Q. And really, to know whether it is going to cross the blood brain barrier, you need to test it to see if it gets to the site of action. Correct?
>
> A. Correct.

Trial Tr. 350:3-6 (Long).

75. Neither Dr. Long nor Dr. Jenner was able to identify any publication before the filing of the '860 patent reporting that ropinirole hydrochloride entered the brain. *See* Trial Tr. 576:23-577:1 (Jenner); 347:23-348:15 (Long). Furthermore, Dr. Long could not point to any testing that was conducted on ropinirole hydrochloride prior to the invention at issue to determine whether the compound crossed the blood-brain barrier. *See* Trial Tr. 350:7-13 (Long).

76. While Teva contends that one of ordinary skill in the art could have predicted the ability of ropinirole hydrochloride to cross the blood-brain barrier based on its alleged oral-

effectiveness and/or lipid solubility ("lipophilicity"), *see* Trial Tr. 199:25-200:7 (Long), the record evidence does not support that contention. Dr. Long acknowledged that there are orally-effective compounds, such as penicillin, that do not cross the blood-brain barrier. *See* Trial Tr. 229:24-231:1 (Long). With respect to lipophilicity, Teva offered no empirical evidence that ropinirole hydrochloride is lipophilic. *See* Trial Tr. 340:10-14 (Long). Furthermore, Dr. Long conceded that not all lipophilic compounds cross the blood-brain barrier and recognized one compound, domperidone, as a specific example of one that does not. *See* Trial Tr. 349:13-23 (Long). Moreover, Dr. Jenner testified that one could not predict based on lipophilicity alone whether a compound would cross the blood-brain barrier. *See* Trial Tr. 553:22-25 (Jenner).

D. The '808 Patent

77. The '808 patent is specifically identified on the face of the '860 patent as one of the "references cited" therein. '860 patent; *see also* Trial Tr. 665:2-16 (Jenner).

78. GSK's '808 patent is directed to certain compounds, such as ropinirole hydrochloride, that are selective, peripheral D2-agonists and, thus, have activity at the pre-synaptic D2 receptors in the peripheral nervous system. *See* '808 patent, Col. 4, ll. 31-44 (PTX 13); Trial Tr. 556:6-557:20 (Jenner). The '808 patent discloses that these compounds "have utility, as specific dopamine agonists, in the treatment of disorders of the cardiovascular system, especially to treat hypertension, to treat angina pectoris, to treat the symptoms of congestive heart failure, or to improve kidney function." '808 patent, Col. 4, ll. 26-30 (PTX 13). Those conditions are associated with the peripheral nervous system. *See* Trial Tr. 322:17-323:9 (Long).

79. While Teva contends that the '808 patent discloses that ropinirole hydrochloride has central, as well as peripheral, D2 activity, the plain language of the patent does not support that interpretation. While claim 8 of the '808 patent (a claim which is not asserted by GSK in

this action) refers to "D2 receptor agonist activity," '808 patent, Col. 10, ll. 52-53 (PTX 13), the specification of the patent specifically defines the term "D2 receptor" to include only peripheral, pre-synaptic D2 receptors. The patent reads: "Otherwise speaking, the main focus of action is at the presynaptic alpha-dopaminergic receptors which may also be called, 'D2 receptors.'" '808 patent, Col. 4, ll. 38-40 (PTX 13). The term "alpha dopaminergic receptors" refers to peripheral nervous system receptors. *See* Trial Tr. 327:6-8 (Long); 556:23-16 (Jenner). The '808 patent thus clearly conveyed to one of ordinary skill in the art that ropinirole hydrochloride acts on pre-synaptic D2 receptors in the periphery. *See* Trial Tr. 556:23-559:3 (Jenner).

80. The '808 patent does *not*: (a) make any mention of Parkinson's Disease; (b) state that ropinirole hydrochloride crosses the blood-brain barrier or has central nervous system activity; or (c) state that ropinirole has activity at post-synaptic dopamine receptors. *See* '808 patent (PTX 13); Trial Tr. 555:21-556:5; 559:7-15 (Jenner); 324:5-7; 300:18-24; 327:12-14 (Long).

81. The '808 patent further does not include any tests showing central nervous system activity. *See* '808 patent (PTX 13). While the patent does contain data from a test known as the rabbit ear artery test, *see* '808 patent, Col. 4, ll. 45-63 (PTX 13), by 1987 those of ordinary skill in the art knew that the rabbit ear artery test was a test for *peripheral* D2 activity. *See* Trial Tr. 327:24-328:2; 328:9-11 (Long). As of May 1987, one of ordinary skill in the art would not have

used the rabbit ear artery test to test for anti-Parkinsonian activity. *See* Trial Tr. 564:10-13 (Jenner).[10/]

E. The 1985 Gallagher Article

82. A 1985 publication by Gregory Gallagher (the named inventor of the '808 patent) and others would have taught one of ordinary skill in the art away from the conclusion that ropinirole hydrochloride would cross the blood-brain barrier. *See* Gallagher, Jr., G., et al., *4-[2-(Di-n-propylamino)ethyl]-2(3H)-indolone: A Prejunctional Dopamine Receptor Agonist,* J. Med. Chem., 28, 1533-36 (1985) ("the 1985 Gallagher article") (PTX 17). The 1985 Gallagher article discusses ropinirole, which is referred to in the publication as "compound 1(c)." *See* 1985 Gallagher article at 1535 (PTX 17); Trial Tr. 574:9-20 (Jenner). The article describes a number of tests conducted on ropinirole and concludes: "These results indicate that 1(c) [ropinirole] *does not produce the central behavioral effects often seen with dopamine agonists*." 1985 Gallagher article at 1535 (PTX 17) (emphasis added). Neither Dr. Jenner nor Dr. Long was aware of any publication reporting any contrary conclusion prior to May 21, 1987. *See* Trial Tr. 344:20-345:2 (Long); 574:25-575:10 (Jenner).

10/ Teva's attempt to rely on a 1978 article by Steinsland, *et al.*, to suggest that one of ordinary skill in the art as of May 1987 would have understood that the rabbit-ear artery test could be used as a measure of anti-Parkinson's activity is misplaced. *See* Steinsland, O. S., *et al.*, *Dopaminergic inhibition of adrenergic neurotransmission as a model for studies on dopamine receptor mechanisms*, Sci., 199(4327), 443-45 (1978) ("1978 Steinsland article") (DTX 172); Trial Tr. 192:17-196:7 (Long). As explained by Dr. Jenner (and conceded by Dr. Long on cross-examination) the 1978 Steinsland article addresses the testing of dopamine *antagonist* compounds (which, as noted in paragraph 55 above, are not anti-Parkinson's candidates) rather than dopamine agonists, and it makes no mention of activity at D2 receptors, which had not even been classified as of 1978. *See* Trial Tr. at 563:25-564:2 (Jenner); 329:10-18; 331:3-15 (Long). The statement at the end of the 1978 Steinsland article concerning the potential use of the rabbit ear artery test to identify potential anti-Parkinson's agents was pure conjecture, and it was known by May 1987 that the rabbit ear artery test was not useful for that purpose. *See* Trial Tr. 564:10-13 (Jenner).

83. In support of the conclusion that ropinirole does not produce central behavioral effects, the 1985 Gallagher article states:

> Unlike apomorphine it [ropinirole] did not increase confinement motor activity (CMA) upon intraperitoneal administration to conscious rats but actually produced some depression of CMA at high doses (>1 mg/kg).

1985 Gallagher article at 1535 (PTX 17). Apomorphine is a dopamine agonist drug known to be effective on post-synaptic receptors in the central nervous system (i.e., those involved in treating Parkinson's Disease). *See* Trial Tr. 575:22-25 (Jenner). Thus, as of 1985, it had been reported that ropinirole showed different results than a known post-synaptic central dopamine agonist in a test of central behavioral effects. *See* Trial Tr. 340:15-17 (Long).[11/]

F. The Cannon 1981 and Cannon 1986 Articles

84. Teva claims that claim 3 of the '860 patent is obvious in light of writings by Dr. Long and his colleague, Dr. Cannon, about a compound that was referred to throughout the trial as "Compound 9." Compound 9 is discussed in the Cannon 1981 Article (DTX 62) and the Cannon 1986 article (DTX 179). The essence of Teva's argument is that, based on the reported activity of Compound 9 in those publications (in combination with the information about ropinirole hydrochloride in the '808 patent), one of ordinary skill in the art would have been able to reasonably predict as of May 1987 that ropinirole hydrochloride would be useful in treating Parkinson's Disease.

85. Teva's reliance on these references is unavailing for four main reasons:

(a) evidence at trial demonstrated that one of ordinary skill in the art at the time of the '860

11/ The decrease in confinement motor activity reported in the 1985 Gallagher article would not have led one of ordinary skill in the art as of May 1987 to conclude that ropinirole could be an effective drug on central dopamine receptors. *See* Trial Tr. 576:5-10 (Jenner). A decrease in motor activity can result from various factors other than dopaminergic activity in the brain, such as a fall in blood pressure, a change in heart rate, a toxic dose, muscle relaxation, or local anesthetic activity. *See* Trial Tr. 345:3-23 (Long); 576:16-22 (Jenner).

patent application would have known that Compound 9 was *not* a viable anti-Parkinson's agent; (b) one of ordinary skill in the art would have known at the time that predictions about the activity of ropinirole hydrochloride could not reliably be made based on the activity of Compound 9, which belonged to a different chemical series; (c) there were competing theories at the time about the structure necessary to interact with dopamine receptors; and (d) the contemporaneous words and actions of Dr. Long and his colleague, Dr. Cannon—both preeminent experts in the field—contradict Teva's claim that their writings rendered the invention at issue here obvious.

86. First, the record evidence contradicts Teva's contention, *see* Trial Tr. 182:2-184:10 (Long), that one of ordinary skill in the art as of May 1987 would have recognized Compound 9 as a potential anti-Parkinson's agent. On cross-examination, Dr. Long conceded that his and Dr. Cannon's theory about Compound 9 was "a guess at the time." Trial Tr. 279:13-17 (Long). Furthermore, contemporaneous publications by Dr. Long, as well as the trial testimony of both Dr. Long and Dr. Jenner, make clear that Compound 9 must be metabolically activated into another compound in order to act as a dopamine agonist.[12/] *See* 1981 Future Directions article at 1117 (PTX 117); Cannon, J.G., et al., *6-Hydroxy-4-[2-di-n-propylamino)ethyl] indole: Synthesis and Dopaminergic Actions*, J. Med. Chem., 27(3), 386-89

12/ Metabolic activation means converting a molecule that is inactive to a compound that is pharmaceutically active through enzymatic alteration of the structure of the molecule. *See* Trial Tr. 580:13-17 (Jenner). Publications in the 1980s suggested that Compound 9 was metabolically activated by hydroxylation (i.e, the addition of a functional group containing an OH group, consisting of an oxygen and a hydrogen). *See* 1981 Future Directions article at 1117 (PTX 117); Trial Tr. at 579:4-580:20 (Jenner). Ropinirole hydrochloride does not have an OH group. *See* Trial Tr. at 580:21-22 (Jenner).

(1984) ("1984 Cannon Article") (PTX 156) at 388;[13/] Trial Tr. 354:4-16 (Long); 578:1-11, 578:17-25 (Jenner). The results of tests published by Dr. Long and his colleagues in 1984 revealed to one of ordinary skill in the art that Compound 9 was not, by itself, active as a dopamine agonist and, if anything, was a weak dopamine *antagonist*. *See* 1984 Cannon article at 388 (PTX 156); Trial Tr. 583:5-585:6 (Jenner). At the time, one of ordinary skill in the art would have known that dopamine antagonist drugs were *not* useful in the treatment of Parkinson's Disease. *See* Trial Tr. 585:7-20 (Jenner).

87. Second, even if Compound 9 were thought to be a promising anti-Parkinson's candidate at the time (which it was not), one of ordinary skill in the art would not have been able to predict the activity of ropinirole hydrochloride based on Compound 9's activity. Compound 9 and ropinirole hydrochloride are not part of the same chemical class or series. *See* Trial Tr. 587:25-588:2 (Jenner); 248:8-11 (Long). Compound 9 is part of the "indole" series of compounds, whereas ropinirole hydrochloride belongs to a series of compounds known as "indolones." *See* Trial Tr. 242:19-20; 243:5-8 (Long). Indoles and indolones differ in terms of: (a) their respective structures and electronic configurations, *see* Trial Tr. 248:12-16 (Long); 459:19-460:7; 473:15-475:4 (Bartlett); (b) their proton-donating capabilities, *see* Trial Tr. 249:7-17 (Long); (c) their hydrogen bonding characteristics and acidity, *see* Trial Tr. 472:18-473:8 (Bartlett); and (d) their lipophilicity, *see* Trial Tr. 480:17-481:20 (Bartlett). The differences between indoles and indolones can have a dramatic effect on their respective ability to bind with receptors. *See* Trial Tr. 479:8-12 (Bartlett).

13/ Compound 9 is referred to as Compound 17 in the 1981 Future Directions article (PTX 117) and as Compound 1 in the 1984 Cannon article (PTX 156). *See* Trial Tr. at 579:4-580:1; 581:19-582:17 (Jenner).

88. One of ordinary skill in the art in the 1980s could not have predicted whether one series of compounds would be dopaminergically active based upon the activity of a different chemical series. *See* Trial Tr. 587:8-24; 594:16-595:7 (Jenner); 262:24-264:7; 258:22-259:4 (Long); Cannon 1986 article at 173 (DTX 179). Structure-activity relationships are a tool used by medicinal chemists to retrospectively relate the activity of a compound to its chemical structure. *See* Trial Tr. 528:19-22 (Jenner). Teva's expert, Dr. Long, conceded that structure-activity relationships with respect to one series of compounds do not necessarily translate to another series of compounds. *See* Trial Tr. 258:22-259:4 (Long). He further conceded that, as of 1987, the structure-activity relationships of dopamine agonists were "exquisitely subtle and not yet understood." Trial Tr. 271:21-272:6 (Long).

89. The Cannon 1986 article relied on by Dr. Long and Teva in support of their obviousness attack emphasizes the limitations of using structure-activity relationships to predict dopamine agonist activity:

> I believe that the results of our twenty years of active study of dopamine permit us to make some conclusions: *Probably many, if not most, of the dopaminergic agonist structure-pharmacology correlations that have been made in the past (by us and by others) are naïve and do not necessarily reflect the true nature of dopaminergic agonist-receptor interactions, even though we can frequently use these correlations rationally to design biologically active compounds.*

Cannon 1986 article at 173 (DTX 179) (emphasis added). At trial, Dr. Long acknowledged the accuracy of that statement. *See* Trial Tr. 267:18-269:5 (Long).

90. The Cannon 1986 article further states:

> Different chemical series of dopaminergic agonists may be interacting with the same geographic area on the receptor protein molecule but, depending upon the chemical nature of the specific chemical series of agonists, a different conformation of the receptor protein may be involved. *Thus, within a given chemical series of agonists, there may be a well defined structure-activity and stereochemical correlation. But these correlations may disappear when a different chemical series of agonists is addressed, and a new combination of structural parameters and stereochemical requirements may apply. If this be*

> *true, structural comparisons and correlations between ergoline derivatives, apomorphine derivatives, and other dopaminergic agonist molecular systems may not only be meaningless, but actually may be misleading.*

Cannon 1986 article at 173 (DTX 179) (emphasis added). Both Dr. Long and Dr. Jenner acknowledged that these statements accurately summarized the state of the art at the time. *See* Trial Tr. 260:10-265:12 (Long); 588:7-589:4.

91. Third, during the time period in which Dr. Cannon and Dr. Long were writing about Compound 9, other medicinal chemists were publishing competing theories about the structural requirements necessary to interact with the dopamine receptor. *See* Trial Tr. 589:13-23; 577:9-22 (Jenner); 277:15-18; 278:4-9 (Long); *see also* Cannon 1986 article at 173 (DTX 179). In light of these competing theories, "one of ordinary skill [in] the art, at that time, would not have been able to reach any firm conclusion about the structural activity requirements necessary to produce a molecule with dopamine agonist activity." Trial Tr. 590:4-13 (Jenner).

92. Fourth, the actions of Dr. Long and his colleague, Dr. Cannon, in the 1980s evidence the fact that their writings about Compound 9 would not have led one of ordinary skill in the art to identify ropinirole hydrochloride as a potential candidate for treating Parkinson's Disease. Drs. Long and Cannon were experts in the study of dopaminergic compounds at the time. *See* Trial Tr. 236:18-21 (Long). They authored numerous publications and investigated approximately 150 different dopamine agonist compounds, specifically for anti-Parkinson's activity. *See* Trial Tr. 238:25-239:9 (Long). They studied numerous series of compounds for anti-Parkinson's activity but never studied or wrote about studying any indolone, including ropinirole hydrochloride. *See* Trial Tr. 239:13-242:18; 243:17-244:22; 245:11-14 (Long).[14/] In

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[14/] Dr. Long admitted on cross-examination that he certainly would have published if he had found a compound or class of compounds that was a candidate for the treatment of Parkinson's Disease. *See* Trial Tr. 253:20-254:2 (Long).

fact, Drs. Cannon and Long actually rejected the idea of pursuing an indolone during the relevant time period because they felt "it wasn't worth [the] time" of one of their graduate students. Trial Tr. 250:7-251:6 (Long).[15/]

93. In light of the record evidence that (a) it was known in the 1980s that Compound 9 did not (by itself) possess the characteristics of a dopamine agonist, (b) Compound 9 was part of a different chemical series than ropinirole hydrochloride, (c) it was understood as early as 1986 that structure-activity relationships could not be translated from one chemical series to another, (d) there were competing theories at the time about the structural requirements needed for dopamine agonist activity, and (e) preeminent experts in the field, such as Drs. Cannon and Long, did not consider or test any indolone compound as an anti-Parkinson's agent, the writings by Dr. Cannon and Dr. Long about Compound 9 would not (alone or in combination with other references) have led one of ordinary skill in the art to reasonably expect that ropinirole hydrochloride could be used to treat Parkinson's Disease.

G. The Cannon 1978 Article

94. Teva also contends that claim 3 of the '860 patent is obvious based, in part, on the Cannon 1978 article (DTX 160), which discusses certain compounds that act on both peripheral and central D2 receptors. *See* Trial Tr. 178:19-179:2 (Long). That argument fails because the 1978 article deals with a different series of compounds than the indolone series, and because the article expressly acknowledges that peripheral and central dopamine receptors may differ.

95. First, the Cannon 1978 article describes the dopamine agonist activity of a series of compounds known as n,n-disubstituted dopamine derivatives. *See* Trial Tr. 590:19-592:4

15/ Dr. Long also testified that, as far as he knew, none of the "maybe 300-400" people who would have met his definition of one of ordinary skill in the art in 1987 synthesized ropinirole or suggested that it could be useful in treating Parkinson's Disease. Trial Tr. 257:18-258:18 (Long).

(Jenner). Ropinirole hydrochloride does not fall within that chemical class. *See* Trial Tr. 592:1-7 (Jenner). One of ordinary skill in the art would not have concluded anything about the activity of ropinirole hydrochloride from the Cannon 1978 article because it addresses a different series of compounds. *See* Trial Tr. 592:22-593:6 (Jenner). As emphasized in the Cannon 1986 article (DTX 179) and described more fully above, one of ordinary skill in the art as of 1987 would have known that "you cannot make a jump from one class of chemical compound to another when attempting to predict dopamine agonist activity." Trial Tr. 594:16-595:6 (Jenner).

96. Second, the Cannon 1978 article contains the following statement:

> It is interesting to attempt some comparison between the actions of the symmetrically n,n-disubstituted homologues of dopamine on peripheral and central mechanisms. *First, it is tentatively suggested that the requirements for peripheral and central dopamine receptor stimulation may differ*; for example, the ability to inhibit stimulation of the cardioaccelerator nerve decreased from methyl to propyl, whereas behavioral effects characteristic of cerebral dopamine receptor stimulation induced by peripheral drug administration decreased from propyl to methyl. Second, the present data give the first indication that the dopamine receptors within the area postrema may differ from those within the periphery and other areas of the brain in their selectivity for only one homologue.

Cannon 1978 article at 251 (DTX 160). This paragraph would have told one of ordinary skill in the art at the time that peripheral and central dopamine receptors were different. *See* Trial Tr. 593:13-594:15 (Jenner). Indeed, Dr. Long acknowledged that, as of 1987, one of ordinary skill in the art would have understood that the requirements for peripheral and central dopamine receptor stimulation may differ. *See* Trial Tr. 302:1-5 (Long).

97. Accordingly, the mere fact that ropinirole hydrochloride was a known *peripheral* D2 agonist and that certain compounds in a different chemical series had been shown in the Cannon 1978 article to have both peripheral and central activity would not have led one of ordinary skill in the art to reasonably expect that ropinirole hydrochloride could be useful in treating Parkinson's Disease.

H. Secondary Considerations of Nonobviousness

1. Commercial Success

98. REQUIP has been commercially successful as a treatment for Parkinson's Disease. *See* Expert Report of Dr. Christopher Vellturo ("Vellturo Report") ¶ 60 (PTX 304); Transcript of the Deposition of Dr. Christopher Vellturo,[16] October 26, 2006 ("Vellturo Dep. Tr."), 111:14-25, 124:19-125:15 (Exhibit B hereto); Expert Report of Harry Boghigian (Boghigian Report") ¶ 55 (DTX 361); Transcript of the Deposition of Harry C. Boghigian,[17] October 31, 2006 ("Boghigian Dep. Tr.) 133:21-134:22 (Exhibit C hereto).[18] Although there is some disagreement between the parties' experts about how best to measure commercial success, there is no dispute that REQUIP has generated substantial revenues. From its inception through the end of August 2006, REQUIP has generated more than $740 million in net sales in the United States. *See* Vellturo Report ¶¶ 24, 49, and Ex. 13 thereto (PTX 304); *see also*, Vellturo Dep. Tr. 129:20-131:7. In addition to its sales in the U.S., REQUIP has generated $557 million in revenue in Europe and the rest of the world between 1999 and 2005. *See* Vellturo Report ¶ 25, and Ex. 10 thereto (PTX 304).[19] Accordingly, through August 2006, REQUIP has generated

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16/ A copy of the relevant pages of Dr. Vellturo's transcript is attached hereto as Exhibit B.

17/ A copy of the relevant pages of Dr. Boghigian's transcript is attached hereto as Exhibit C.

18/ As described in paragraph 18 above, with the Court's permission the parties stipulated to the submission of the expert reports and deposition transcripts of Dr. Vellturo and Mr. Boghigian in lieu of live testimony.

19/ REQUIP's sales in the United States, even without considering its performance in the rest of the world, evidence its commercial success.

nearly $1.3 billion in worldwide net sales (i.e., $740 million + $557 million). Teva's expert, Mr. Boghigian, does not dispute these numbers.[20/]

99. Mr. Boghigian prefers to measure commercial success by reference to prescriptions, rather than sales dollars. By this measure too, REQUIP has achieved commercial success. Teva's clinical expert, Dr. Tarsy, acknowledged that REQUIP is widely prescribed for Parkinson's Disease. *See* Trial Tr. 127:17-23 (Tarsy). Moreover, according to Mr. Boghigian's expert report, in each year since 2004, REQUIP has been the most prescribed dopamine agonist for the treatment of Parkinson's Disease in the United States. *See* Boghigian Report, Ex. D (DTX 361). Mr. Boghigian's data shows that, during that same time period, REQUIP has been second only to levodopa among drugs prescribed in the United States for the treatment of Parkinson's Disease. *See id.*[21/]

100. REQUIP's share of the market, in terms of both dollars and prescriptions, grew considerably from 1999-2005. In fact, during that period, REQUIP's growth significantly outpaced both the market for all Parkinson's Disease drugs and the market for levodopa in

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[20/] Dr. Vellturo further opined that REQUIP has contributed significant profits to GSK, of at least approximately $250 million in net income from 1997 through August 2006. *See* Vellturo Report ¶ 55 (PTX 304). While Mr. Boghigian takes issue with the methodology Dr. Vellturo used to calculate REQUIP profits, this dispute is immaterial because the revenues and prescription data for REQUIP, along with opinions offered by each party's clinical expert concerning the success and effectiveness of the drug, are sufficient to establish commercial success even without any consideration of profits.

[21/] Mr. Boghigian relied on data from Verispan that purported to distinguish between prescriptions for Parkinson's Disease and prescriptions for Restless Legs Syndrome. *See* Boghigian Report ¶22. Dr. Vellturo, however, did not believe this data should be relied upon, because of the small number of Restless Legs Syndrome prescriptions prior to FDA approval in 2005. *See* Vellturo Dep. Tr. 178:8-180:15. In any case, both experts agree that, prior to the approval of REQUIP for the treatment of Restless Legs Syndrome in 2005, most of REQUIP's sales were for the treatment of Parkinson's Disease. *See* Vellturo Report ¶ 61 (PTX 304); Boghigian Report ¶¶ 16, 32 (DTX 361); Boghigian Dep. Tr. 209:11-210:3.

particular. *See* Vellturo Report ¶¶ 21-23, and Exs. 7-A – 8-C thereto (PTX 304). The same is true for the period Mr. Boghigian believes is more appropriate, 1999-2004. *See* Boghigian Report ¶ 33 and Ex. F thereto (DTX 361); Vellturo Report n.37 (PTX 304).

101. REQUIP cannot be used for the treatment of Parkinson's Disease without practicing the invention claimed in the '860 patent. REQUIP's commercial success, therefore, has a substantial nexus to its use in the treatment of Parkinson's Disease. *See* Vellturo Report, ¶¶ 58-63; ¶¶ 15-20 (PTX 304). In fact, Mr. Boghigian found that REQUIP's effectiveness in the treatment of Parkinson's Disease was essential to its commercial success:

Q. Mr. Boghigian, is Requip effective for the treatment of Parkinson's disease?

A. Yes.

Q. Without that effectiveness, would the commercial success that you have observed for Requip have been possible?

A. Without that the product never would have been approved by the FDA.

Q. So the commercial success would not have been possible; is that right?

A. There wouldn't have been any opportunity for commercial success.

Q. So effectiveness, it's fair to say, is essential to achieving any commercial success in the pharmaceutical industry?

A. That's correct.

Q. Is effectiveness derived from the intrinsic properties of the compound ropinirole hydrochloride?

A. Yes.

Boghigian Dep. Tr. 168:16-169:15.

102. Despite finding that REQUIP's effectiveness in the treatment of Parkinson's Disease—which is the invention claimed in the '860 patent—was "essential" to its commercial success, Mr. Boghigian did not find a "nexus" between that effectiveness and commercial success. The "nexus" test offered by Mr. Boghigian, however, is one under which a nexus could

never be established for any marketed drug. At his deposition, Mr. Boghigian testified as follows:

Q. Okay. And how could one establish that a nexus exists under your approach?

A. Have the product approved and not do anything and see what happens.

Q. You mean no marketing?

A. Right

Q. Is it your experience that pharmaceutical products that are patented are ever released onto the market without any marketing or promotional activities?

A. Not to my knowledge.

Q. So you don't have – can you think of an example in which this nexus has actually been established with respect to a product?

MR. KAY: Objection.

A. What nexus?

Q. The nexus between the commercial success of the product and the patent?

A. I can't think of any situation where it's happened with a prescription pharmaceutical product.

Boghigian Dep. Tr. 279:11-280:8. Mr. Boghigian's nexus test, which would essentially eliminate the commercial success inquiry for all marketed products, should be rejected.

103. The testimony offered by both parties' clinical experts, Dr. Sudarsky and Dr. Tarsy, further demonstrates the commercial success of REQUIP and the substantial nexus between that success and the invention at issue. Both experts opined that REQUIP is useful, effective, and beneficial to have as a treatment option for Parkinson's Disease. *See* paragraph 42, *supra*. Teva's expert, Dr. Tarsy, acknowledged that REQUIP has helped the patients for whom he has prescribed it and that, if it was not effective, he would withdraw the drug. *See* Trial Tr. 126:20-127:3 (Tarsy). Dr. Tarsy further acknowledged that REQUIP is successful, and

both clinical experts agreed that there is room on the market for more than one successful Parkinson's Disease drug. *See* Trial Tr. 131:24-132:6; 146:14-16 (Tarsy); 430:15-22 (Sudarsky).

2. Long-Felt Need

104. As of May 1987, there was a long-felt need for alternative Parkinson's Disease treatments. Teva's pharmacology expert, Dr. Long, agreed that there was a need for an alternative to levodopa back in the 1980s. *See* Trial Tr. 253:16-19 (Long). Teva's clinical expert, Dr. Tarsy, testified that problems associated with levodopa have been known since the 1970s, and that researchers were trying to find better drugs to solve those problems at the time. *See* Trial Tr. 128:5-23 (Tarsy). Dr. Tarsy also testified that problems with the ergoline dopamine agonists were known in the 1980s and that researchers at that time were looking for alternative treatments for Parkinson's Disease. *See* Trial Tr. 131:10-18 (Tarsy). REQUIP presents just such an alternative.

105. Moreover, with respect to the treatment of Parkinson's Disease generally, it is useful to have more than one available drug. *See* Trial Tr. 125:16-18 (Tarsy); 429:24-430:22 (Sudarsky). The disease goes on for a long time, patient response is variable, and there are patients who, for one reason or another, might do better on one drug versus another. *See* 429:24-430:22 (Sudarsky); Trial Tr. 125:5-15 (Tarsy). Therefore, the addition of REQUIP to the array of available medicines satisfied a long-felt need for alternative Parkinson's Disease treatments.

3. Failure of Others

106. The failure of others, particularly experts in the study of dopaminergic agents, to identify ropinirole hydrochloride as a potential anti-Parkinson's treatment further evidences the nonobviousness of this invention. As described more fully in paragraph 92 above, Teva's expert, Dr. Long, and his colleague, Dr. Cannon, were preeminent experts in the field who authored numerous publications and investigated approximately 150 different dopamine agonist

compounds, specifically for anti-Parkinson's activity. *See* Trial Tr. 238:25-239:9 (Long). Yet they never studied or wrote about studying any indolone, including ropinirole hydrochloride. *See* Trial Tr. 239:13-242:18; 243:17-244:22; 245:11-14 (Long). The inability of experts who devoted a significant portion of their careers to the study of dopamine agonists and anti-Parkinson's agents to identify ropinirole hydrochloride as a potenital Parkinson's Disease therapy demonstrates the nonobviousness of the invention at issue in claim 3 of the '860 patent.[22/]

4. Copying

107. Teva's corporate representative, Ms. Jaskot, testified that the drug Teva seeks to market would have the same active ingredient as REQUIP, i.e., ropinirole hydrochloride. *See* Trial Tr. 76:22-77:3 (Jaskot). She further testified that Teva performs bioequivalence testing to "make sure we are substitutable for the brand reference product." Trial Tr. 72:1-3 (Jaskot). Teva's plans to market a "substitute" for REQUIP that has the same patented active ingredient amounts to copying, another indication of the nonobviousness of claim 3 of the '860 patent.

22/ The actions of Teva itself provide further evidence of failure of others. Teva's corporate representative, Deborah Jaskot, testified that a Teva entity (Teva Neurosciences) was involved in innovative research and development in the area of the central nervous system for almost two decades. *See* Trial Tr. 84:16-85:6) (Jaskot). There is no evidence that any Teva scientists thought about using ropinirole hydrochloride, or any indolone, for the treatment of Parkinson's Disease before May 1987. *See* Trial Tr. 85:7-86:12 (Jaskot).

CONCLUSIONS OF LAW

I. LEGAL STANDARDS

A. Validity

108. A duly issued patent is presumed valid. Each claim of a patent (whether in independent, dependent, or multiple dependent form) shall be presumed valid independently of the validity of other claims. *See* 35 U.S.C. § 282.

109. The burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity. 35 U.S.C. § 282. One seeking to prove a patent is invalid must do so by clear and convincing evidence. *See, e.g., Kahn v. Gen. Motors Corp.*, 135 F.3d 1472, 1480 (Fed. Cir. 1998).

B. Anticipation

110. Anticipation is a question of fact. *See, e.g., Rapoport v. Dement*, 254 F.3d 1053, 1057-58 (Fed. Cir. 2001).

111. A patent is anticipated under 35 U.S.C. § 102(b) if "the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States . . . ." 35 U.S.C. § 102(b) (2000); *Minnesota Mining & Mfg. Co. v. Chemque, Inc.*, 303 F.3d 1294, 1301 (Fed. Cir. 2002).

112. For prior art to anticipate under 35 U.S.C. § 102(a) because it is "known," the knowledge must be publicly accessible, and it must be sufficient to enable one with ordinary skill in the art to practice the invention. *Minnesota Mining & Mfg. Co.*, 303 F.3d at 1301.

113. A patent is invalid for anticipation if a single prior art reference discloses each and every limitation of the claimed invention. *See Lewmar Marine, Inc. v. Barient Inc.*, 827 F.2d 744, 747 (Fed. Cir. 1987); *In re Paulsen*, 30 F.3d 1475, 1478-79 (Fed. Cir. 1994). A prior art

reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference. *See Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003); *Continental Can Co. U.S.A., Inc. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 2001).

C. Obviousness

114. Whether a patent is obvious is a question of law based upon underlying factual questions. *See Richardson-Vicks v. Upjohn Co.*, 122 F.3d 1476, 1479 (Fed. Cir. 1997); *see also Karsten Mfg. Corp. v. Cleveland Golf Co.*, 242 F.3d 1376, 1384 (Fed. Cir. 2001).

115. A patent is invalid as obvious "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a); *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1360 (Fed. Cir. 2006).

116. The standard obviousness inquiry requires specific factual findings on: (1) the scope and content of the prior art; (2) the level of ordinary skill in the field of invention; (3) differences between the claimed invention and the prior art; and (4) objective indicia of non-obviousness. *See Graham*, 383 U.S. at 17-18; *Yamanouchi Pharm. Co. v. Danbury Pharmcal, Inc.*, 231 F.3d 1339, 1343 (Fed. Cir. 2000).

117. The use of hindsight is inappropriate in determining whether an invention is obvious; rather, courts must be careful to "guard against slipping into use of hindsight and to resist the temptation to read into the prior art the teachings of the invention in issue." *Graham*, 383 U.S. at 36; *see also ADT Corp. v. Lydall, Inc.*, 159 F.3d 534, 546 (Fed. Cir. 1998); *Dystar*, 464 F.3d at 1360.

118. Obviousness also requires one of ordinary skill in the art to have a reasonable expectation of success as to the invention. "[O]bvious to try" and "absolute predictability" are incorrect standards. *In re O'Farrell,* 853 F.2d 894, 903 (Fed. Cir. 1988). The presence of a reasonable expectation of success is measured from the perspective of a person of ordinary skill in the art at the time the invention was made, *Life Techs., Inc. v. Clontech Labs., Inc.,* 224 F.3d 1320, 1326 (Fed. Cir. 2000), and is a question of fact, *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1164-65 (Fed. Cir. 2006).

D. Secondary Considerations of Nonobviousness

119. Other objective indicia, or "secondary considerations" of nonobviousness are part of the obviousness analysis. Secondary considerations include "commercial success, unexpected results, copying, long-felt but unresolved need, and the failure of others to develop the invention." *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1378 (Fed. Cir. 2005) (citing *Graham*, 383 U.S. at 17-18).

II. ULTIMATE CONCLUSIONS OF LAW AND UNDERLYING FACT

120. Teva has failed to carry its burden of showing by clear and convincing evidence that claim 3 of the '860 patent is invalid as obvious or anticipated.

A. Ordinary Skill in the Art

121. For purposes of this analysis, the more stringent definition of one of ordinary skill in the art advocated by Teva is applied. *See* paragraphs 63-66, *supra*.

B. Anticipation

122. Teva has failed to carry its burden of demonstrating by clear and convincing evidence that claim 3 of the '860 patent is anticipated by the '808 patent, expressly or inherently. As explained in detail above, the '808 patent (which was considered by the United States Patent and Trademark Office and is listed as prior art on the face of the '860 patent) makes no mention

of Parkinson's Disease. Nor does that patent give any indication that ropinirole hydrochloride acts centrally on post-synaptic D2 receptors or crosses the blood-brain barrier, all of which were understood by those of ordinary skill in the art at the relevant time to be essential criteria for a dopamine agonist that could be used to treat Parkinson's Disease. Several cases have established that if the prior art does not contain any disclosure of the use of a known compound for the new patented condition, the prior art does not anticipate. *See Rapoport*, 254 F.3d at 1060-62 (affirming finding that a patent directed to the use of a compound for the treatment of sleep apnea was not anticipated where prior art disclosed using the same compound for anxiety); *Glaxo Group Ltd. v. Teva Pharms. USA, Inc.*, No. 02-219 (GMS), 2004 U.S. Dist. LEXIS 16750, *50-58 (D. Del. Aug. 20, 2004) (finding that an earlier patent directed to the treatment of migraines did not anticipate later patents for nausea and emesis).

123. Moreover, one of ordinary skill in the art could not reasonably have expected the anti-Parkinsonian activity of ropinirole hydrochloride based on the disclosure in the '808 patent that the compound is active at *pre-synaptic* D2 receptors in the *peripheral* nervous system. In the 1980s, there was substantial confusion and unpredictability regarding dopamine receptors and the activity of compounds that acted on them. As of May 1987, there were known examples of compounds that acted peripherally but not centrally, as well as compounds that acted pre-synaptically but not post-synaptically. Furthermore, the ability of a compound such as ropinirole hydrochloride to cross the blood-brain barrier was not reasonably predictable. Indeed, Teva's expert, Dr. Long, conceded that testing would have been necessary to determine whether a peripheral pre-synaptic D agonist would cross the blood-brain barrier and have post-synaptic D2 activity in the brain, as is required to treat Parkinson's Disease. No such data or testing is provided in the '808 patent.

C. Obviousness

124. Teva has also failed to carry its burden of showing by clear and convincing evidence that claim 3 of the '860 patent was obvious in light of the '808 patent in combination with one or more prior art references, including the Cannon 1981, Cannon 1986, and Cannon 1978 articles. This is true regardless of whether the Court applies the Federal Circuit's rigorous "motivation-suggesting-teaching" test as articulated in *Teleflex, Inc. v. KSR Int'l Co.*, 119 Fed. Appx. 282, 286 (Fed. Cir. 2005), or more lenient tests articulated by that court. *See generally, Dystar*, 464 F.3d at 1356; *see also* Trial Tr. 721:23-722:8.

125. The pharmacology experts for both GSK and Teva were in agreement that the classification of dopamine receptors was confusing at the time of the filing of the '860 patent. As of May 1987, one of ordinary skill in the art could not reasonably have expected that activity at a pre-synaptic peripheral D2 receptor would result in activity at a post-synaptic central D2 receptor. Moreover, no publication suggested at the time that ropinirole hydrochloride acted centrally. To the contrary, the 1985 Gallagher article taught that ropinirole hydrochloride did not have central behavioral effects.

126. For the reasons discussed more fully above, the writings of Dr. Cannon and Dr. Long about Compound 9 in the 1981 and 1986 Cannon articles would not have allowed one of ordinary skill in the art to conclude anything about the activity of ropinirole hydrochloride. In summary: (a) it was known at the time the Compound 9 was not, by itself, a dopamine agonist; (b) in any event, conclusions about the activity of ropinirole hydrochloride could not be drawn based on the activity of Compound 9 because it was part of a different chemical series; (c) there were other competing theories at the time about the structure necessary for dopaminergic activity; and (d) even Drs. Cannon and Long, preeminent experts in the field of dopaminergic

compounds, did not conclude based on their own work that ropinirole hydrochloride should be pursued as anti-Parkinson's agent.

127. Similarly, the Cannon 1978 article, alone or in combination with anything else, would not have caused one of ordinary skill in the art to reasonably expect that ropinirole hydrochloride could be useful in treating Parkinson's Disease. That reference expressly acknowledges that peripheral and central dopamine receptors may differ. In addition, the activity of the compounds at issue in the 1978 article would not have enabled one of ordinary skill in the art to have formed any reasonable expectation concerning the activity of ropinirole hydrochloride because those compounds belonged to a different chemical series.

128. In summary, Teva has failed to carry its burden of proving by clear and convincing evidence that claim 3 of the '860 patent would have been obvious to one of ordinary skill in the art at the time of the invention in view of the prior art references and knowledge in the field at the time.

D. Secondary Considerations of Nonobviousness

129. Evidence relating to the secondary considerations of commercial success, long-felt need and failure of others provides additional support for the finding that claim 3 of the '860 patent was not obvious.[23/]

130. In particular, as described in paragraphs 98-107 above, the record evidence establishes that (a) REQUIP satisfied a long-felt but unresolved need for alternative treatments for Parkinson's Disease;[24/] and (b) others tried and failed to develop such alternative treatments.

[23/] In light of Teva's failure to carry its burden of establishing a *prima facie* case of obviousness, GSK does not have the burden of proving that objective indicia of nonobviousness support a ruling in its favor.

131. Copying can also be considered evidence of nonobviousness, even in the ANDA context. *See, e.g., Janssen Pharmaceutica N.V. v. Mylan Pharms., Inc.*, 456 F.Supp.2d 644, 671 (D.N.J. 2006) (considering copying as evidence of non-obviousness in ANDA case); *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 2001 WL 1397304, *14 (S.D. Ind. 2001) (same, but according copying only "a little weight" due to the ANDA context); *but see Eli Lilly & Co. v. Teva Pharms. USA, Inc.*, 2004 WL 1724632, *38 (S.D. Ind. July 29, 2004) (finding that copying in the ANDA context is "not an indication of non-obviousness). To the extent the Court finds such evidence relevant, Teva's attempt to copy the active ingredient in REQUIP further demonstrates the nonobviousness of the invention at issue in claim 3 of the' 860 patent.

132. The commercial success inquiry is not necessary here. As the Federal Circuit has stated, commercial success exists largely for "close cases [involving] subject matter that appears obvious is in law" which may be deemed nonobvious because of its commercial success. *Syntex*, 407 F.3d at 1383 (citing *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005)). As set forth above, the subject matter here does not "appear obvious in law" at all. Accordingly, the commercial success inquiry is not necessary to defeat Teva's obviousness challenge to claim 3 of the '860 patent.

133. In any case, for the reasons set forth in paragraphs 98-103 above, REQUIP is a commercial success. *Merck v. Teva*, 395 F.3d at 1376, does not bar this conclusion. As the Federal Circuit made clear in *Syntex,* 407 F.3d at 1383, *Merck v. Teva* does not state a *per se* rule

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24/ As described above, at the time of the invention at issue here, researchers were looking for alternatives to known Parkinson's Disease treatments (levodopa and ergoline dopamine agonists) due to side effects associated with those treatments. In a case involving similar circumstances – i.e., the invention of a new treatment for migraines that did not present the debilitating side-effects associated with preexisting treatments for that condition – this Court found that the invention satisfied a long-felt need. *See Glaxo Group Ltd v. Teva Pharms. USA, Inc.*, 2004 U.S. Dist. LEXIS 16750, at *40.

against commercial success findings where, as here, there was a prior patent to the active ingredient in the compound at issue. Rather, in light of *Merck v. Teva*, courts are required to consider whether, in light of prior patents, commercial success "may heavily derive from subject matter that does not on the whole contribute to the patentable distinctiveness" of the claims at issue. *Syntex,* 407 F.3d at 1383. In such cases, courts are required to "carefully consider" whether the nexus requirement has been met. *Id.*

134. As described in more detail in paragraphs 101-103 above, there is a substantial nexus between the commercial success of REQUIP and the invention at issue. As explained, above, the '808 patent did not mention or suggest the use of ropinirole hydrochloride for treatment of Parkinson's Disease. The use of this compound for that purpose—which is the invention claimed in the '860 patent—is the reason for its commercial success. The testimony of both the clinicians and the commercial success experts on both sides makes clear that REQUIP is widely prescribed as an anti-Parkinson's agent and that it would not be if it were not effective for that purpose. Accordingly, the nexus requirement is satisfied.

III. CONCLUSION

135. For the foregoing reasons, GSK is entitled to the following relief:

(a) A declaration that the '860 patent is not invalid or unenforceable;[25/]

(b) A declaration that the submission of Teva's ANDA infringes Claim 3 of the '860 patent;

(c) An order providing that the effective date of any approval of Teva's ANDA shall be a date which is not earlier than the expiration of the '860 patent;

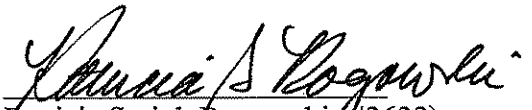
25/ This assumes an outcome favorable to GSK on the issue of inequitable conduct, which, as noted in footnote 1, is the subject of separate briefing.

(d) An order permanently enjoining Teva and its affiliates and subsidiaries, and each of their officers, agents, servants, and employees from the commercial manufacture, use, offer to sell, or sale within the United States or importation into the United States of the products that are the subject of Teva's ANDA and from inducing such conduct by others, until after the expiration of the '860 patent; and

(e) Such further and other relief as this Court deems proper and just.

Respectfully submitted,

SMITH KLINE & FRENCH LABORATORIES LIMITED AND SMITHKLINE BEECHAM CORPORATION, D/B/A GLAXOSMITHKLINE
By their attorneys,



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EXHIBITS A TO C ARE FULLY REDACTED.

CERTIFICATE OF SERVICE

I, Patricia Smink Rogowski, hereby certify that on February 15, 2007 **[PUBLIC VERSION] PLAINTIFF'S PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW** was filed with the Court Clerk using CM/ECF which will send notification of such filing(s) to Josy W. Ingersoll.

I hereby further certify that on February 15, 2007, I have also served this document on the attorneys of record at the following addresses as indicated:

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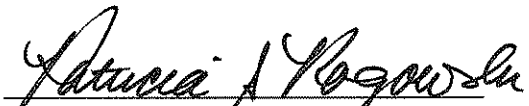

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